THE TYPICAL FEATURES OF MESIAL TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS IN CHILDREN

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ABSTRACT

Purpose. The aim of this study is to report on a group of 30 children with the diagnosis of mesial temporal lobe epilepsy (MTLE) and a magnetic resonance imaging (MRI) evidence of hippocampal sclerosis (HS), with special emphasis on electroclinical features, surgical treatment and prognosis.
Material and methods. The patient's files were retrospectively analyzed. All children underwent a comprehensive presurgical evaluation. We assessed age dependency of different clinical symptoms. The postsurgical outcome was classified using the Engel scale.
Results. 11 cases had a personal history of febrile seizure. The patient's seizure semiology contained a group of symptoms that are age-dependent. Young children presented a predominance of motor arrest, autonomic signs and rare reported auras. In older children and adolescents, the seizure semiology became more elaborated with the presence of aura, emotional expressions, automatisms and motor lateralized signs. The presurgical evaluation confirmed the epileptic focus similar with the MRI localization of hippocampal sclerosis. 20 cases received the surgical treatment and 14 patients (70%) disclosed the postoperative seizure outcome in class I Engel (free of disabling seizures).
Conclusions. MTLE-HS is a clearly define epileptic syndromic entity and the accurate diagnosis of patients that presented the onset in childhood and adolescence has a great influence on the therapeutic decision of their epilepsy.

Key words: mesial temporal lobe epilepsy, hippocampal sclerosis, children

INTRODUCTION

The mesial temporal lobe epilepsy (MTLE) is a well define epileptic syndromic entity, in which spontaneously recurrent seizures are originated in different areas of mesial temporal lobe, particularly in the hippocampus, amygdala and in the parahippocampal gyrus (1). The hallmark lesion of the frequent studied form of MTLE is the hippocampal sclerosis (HS) (2).

In the literature, the majority of data derives from adult studies of mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE- HS), especially in patients with refractory epilepsy (3). Until recently, the characterization of MTLE-HS in children was made in parallel with the data obtained from adults (4). There is still a lack of detailed studies of electroclinical (5, 6) and surgical features (7, 8) of MTLE-HS in pediatric populations.

Retrospective surgical studies highlight the role of "initial precipitating incidents", especially febrile seizures (FS) in the development of HS (9, 10). A history of childhood FS is present in seventy percent of the patients with MTLE-HS (11). Others "initial precipitating incidents" are represented by infection of the central nervous system, head trauma, hypoxia, that usually occurred before the age of 5 years (1). A familial form of MTLE-HS that is a relatively benign epilepsy syndrome with adolescent or adult onset has been recognized (12). Even

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if MTLE-HS can occur also as a clinical phenotype of febrile seizures plus (13), the genetic background in MTLE-HS remains a subject of debate (14).

After the early precipitating incident, there is a characteristic latent and silent period (1). Thus, epileptic seizures in MTLE-HS typically have onset in the first decade of life and initially respond well at medical treatment during the first years of the syndrome (15). Moreover, the transition from the latent period to onset of epileptic seizures establishes the basis for the progression of epileptogenesis in MTLE-HS (16).

The semiology of mesial temporal lobe seizures is similar to that of adults, especially in older children (7). The seizure onset is made by an epigastric aura associated with emotional disturbances and autonomic symptoms. The ictal typical symptomatology is represented by oroalimentary and manual automatisms, a progressive impairment of consciousness and dystonic postures. The presence of the ictal speech is suggestive of the onset in the non-dominant hemisphere. Infants and young children demonstrated different seizure semiology, with the predominance of motor features like infantile spasm and even apnoeic attacks (17).

For an accurate identification of the epileptogenic zone, usually a lot of neuroimaging and functional tests are performed during the presurgical evaluation of the patients. These are video-EEG monitoring, magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), positron emission tomography (PET) and neuropsychological evaluation. Children with MTLE-HS demonstrated anterior temporal interictal epileptiform discharges during the video-EEG monitoring, hippocampal atrophy and/or abnormal signal intensity on MRI and additional evidence of temporal dysfunction correlated with the side of lesion on functional imaging techniques and neuropsychological evaluation (6, 7). In refractory cases, the surgical treatment offers the chance of seizure freedom and may improve cognitive and psychosocial outcome. The postsurgical seizure outcome in children and adolescents is similar to that in adult studies (7, 8).

The vast majority of patient cohorts reported in adult studies of MTLE-HS had onset of their habitual seizures during childhood (1, 11). Nevertheless, there are still many difficulties to identify the characteristic clinical picture of MTLE-HS in children (17). These are explained by the particular electroclinical features of temporal seizures in small children and by the influence of brain maturation during the temporal epileptogenesis.

In this study, we try to present not only the typical features of MTLE-HS in children, but also the impact of the surgical treatment and prognosis.

MATERIAL AND METHODS

We retrospectively reviewed the charts of 30 patients with the diagnosis of MTLE and evidence of HS on MRI that were evaluated in the Pediatric Neurology department of University Hospital Leuven, Belgium between January 2000 and December 2010.

Inclusion criteria were the following:

- Clinical features (aura, motion arrest, alteration of consciousness, autonomic symptoms, automatisms, motor sings, postictal symptoms)
- EEG features (interictal and ictal EEG) demonstrating seizure origin from mesial temporal lobe
- MRI with compatible signs of HS
- SPECT and PET features that confirmed a mesial temporal focus
- Functional MRI for language lateralization
- Neuropsychological evaluation (including memory)
- Neuropathological results that confirmed HS (in surgical cases).
- We excluded patients with MTLE due to other types of lesions like tumors or vascular malformations.

Clinical history (including familial history of epilepsy and febrile seizures, type and age at the initial precipitating incident, presence and duration of latent and silent period, age at onset), surgical treatment, pathological analysis and outcome were reviewed for all patients.

All patients underwent a comprehensive presurgical evaluation with electrophysiological studies (routine scalp EEG, prolonged video-EEG monitoring), brain MRIs, interictal and ictal SPECT, interictal 2-[F]-fluoro-2-deoxy-d-glucose (FDG) PET, functional MRI and neuropsychological evaluation. In surgical cases, the Engel score and age at surgery were evaluated. A minimum postoperative follow-up period of 6 months was available.

Statistical studies

We used Fisher's exact test for the statistical analysis. The test was 2 sided and p-values less than 0.05 were considered as indicating statistical significance.

RESULTS

Gender

There was a slight predominance of boys (16M/14F) between the patients included in study.

Family history of epilepsy and febrile seizures

Nine patients (30%) had a familial history of epilepsy and 4 patients (13.3%) had a history of febrile convulsions. Between these 4 patients, 3 of them experienced also febrile seizures during MTLE-HS.

History of the initial precipitating incidents (IPI)

Four patients (13.3%) presented simple febrile seizures and 6 patients (20%) complex febrile seizures. Another 3 patients (10%) experienced a febrile status epilepticus, as a single event or associated with the complex febrile seizures, so that a total of 11 patients (36.6%) had a history of febrile seizures. The age at presentation of febrile seizures was range between 4 and 29 months (mean 12 months, median 9 months)

Others initial incidents were presented under the form of CNS infections in 2 patients, head trauma in 2 patients and postnatal hypoxia in the context of prematurity in one patient (Figure 1). The age at presentation in IPI patients without seizures ranged between 1 and 31 months (mean 15.6 months, median 12 months).

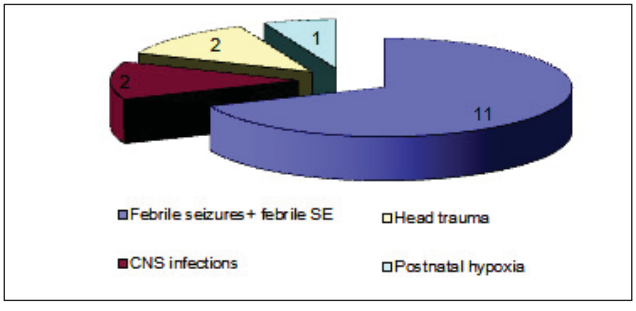

FIGURE 1. *The number of patients with initial precipitating incidents*

The latent period

A latent period is defined by the time period between IPI and the occurrence of the first habitual temporal seizures (1). Sixteen patients demonstrated the presence of a latent period with a mean duration of 39.8 months (range: 2-139 months).

Age of onset

The onset of habitual seizures was between 7 months and 14 years (mean: 4 years, median: 3 years). The patients were grouped in three age groups according with their epilepsy onset: before 2 years of age (8 patients – 26.7%), between 2 and 10 years (20 patients – 66.7%) and after 10 years (2 patients – 6.7%).

Seizure semiology

The semiology was assessed on the basis of the description offered by patient or family and from direct observation during the long-term video-EEG monitoring. The mean age at the time of the video-EEG monitoring was 10 years (range: 4-18 years).

The frequent symptoms that occurred were staring (76% patients), motor lateralized signs (66% patients) and oroalimentary automatisms (43% patients). The frequency of aura (36%) may be underestimated in the affected children because of the subjective implications in its description (Table 1).

The seizures frequency early in the course of the epilepsy was weekly in 8 patients (26.7%), monthly in 19 patients (63,3%) and annually in 3 patients (10%).

TABLE 1. *Critical clinical symptoms during the video-EEG monitoring*

Critical clinical symptoms	Number of patients	Percent (%)
Motor arrest and staring	23	76
Motor lateralized symptoms	20	66
Oro-alimentary automatisms	13	43
Aura	11	36
Contralateral hand dystonia	9	30
Manual automatisms	7	23
Ictal aphasia	7	23
Alteration of consciousness	6	20
Vocalizations	6	20
Autonomic signs	6	20
Emotional signs	3	10
Automatisms with preserved consciousness	2	6
Vomiting	2	6
Ictal speech	2	6
Unilateral blinking	2	6
Urinary urge	2	6

All patients included in this study exhibit complex focal seizures, 7 patients (23.3%) presented also simple focal seizures and 15 patients (50%) presented at least one secondarily generalized tonic-clonic seizure in the evolution of their epilepsy. Furthermore, 13 patients (43.3%) experienced a status epilepticus, even at onset or in the course of their epilepsy.

Correlation between clinical features and age

According to the literature (5, 6, 17) we classified the semiology signs and symptoms in two intervals of age: 0-6 years and 6-18 years (Table 2).

TABLE 2. *Clinical features in relation with age*

Clinical picture	0-6 years		6-18 years		Fisher exact test (p)
	Yes	No	Yes	No	
Epigastric aura	2	28	22	8	0.0001
Fear	1	29	6	24	0.1028
Motor arrest	15	15	24	6	0.0048
Tachycardia	1	29	7	23	0.0523
Ictal aphasia	1	29	5	25	0.1945
Unilateral head and eyes deviation	7	23	14	16	0.1033
Oroalimentary automatisms	6	24	19	11	0.0014
Pallor	4	26	9	21	0.2092
Cyanosis	4	26	1	29	0.3533
Vomiting	3	27	6	24	0.4716

The presence of some of the frequent lateralizing signs like epigastric aura, motor arrest and oroalimentary automatisms are statistically dependent of age (Fig. 5), in contrast with emotional expression and autonomic signs that are independent by age (Fig. 6).

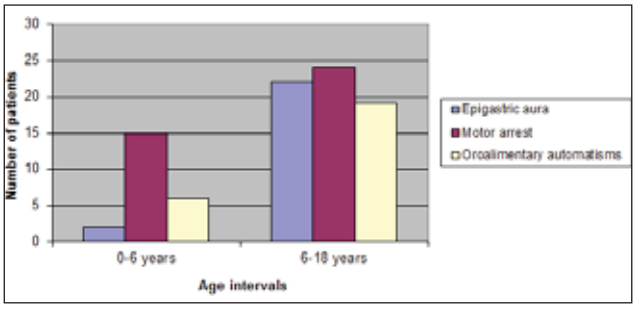

FIGURE 2. *Clinical features dependent of age*

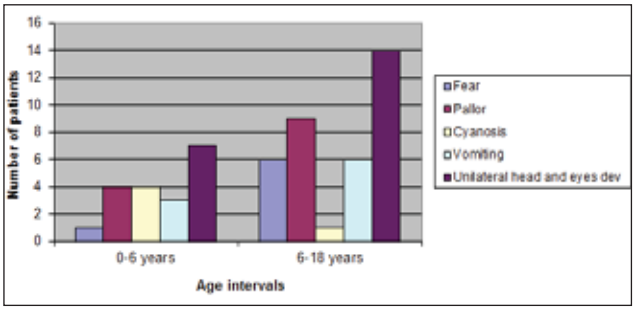

FIGURE 3. *Clinical features independent of age*

The modification of seizures pattern with age was observed, thus, young children presented a predominance of motor arrest, autonomic signs and rare reported auras. In older children and adolescents, the seizure semiology became more elaborated with the presence of aura, emotional expressions, automatisms and motor lateralized signs.

Silent period

The silent period is the time period between the first habitual seizure and the onset of intractability (1). The onset of intractability is extremely difficult to determine in a given point in time, so we used the definition proposed by the International League Against Epilepsy Commission on Therapeutic Strategies. An intractable or drug resistant epilepsy is defined by "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (18).

Three patients did not present a silent period and the other patients exhibited a mean duration of their silent period of 7.8 years (range: 1-17 years).

The neurologic examination

The physical examination was normal in 27 patients (90%) and three patients demonstrated a left hemiparesis. Twenty-seven patients were right-handed (90%) and three patients (10%) were left-handed.

Neuroimaging

All patients presented the defined signs of HS on MRI, so that 28 patients (93.3%) demonstrated unilateral HS (left in 18 and right in 10) and only 2 patients (6.7%) presented bilateral HS (Figure 7). In 22 patients (73.3%) there was increased signal in T2 and FLAIR weight images and in 20 cases (66.6%) hippocampal atrophy. In 12 cases (40%) it was reported both increased signal and unilateral hippocampal atrophy. In 4 cases (13.3%) the neuroradiological description reported only the HS and in 3 cases (10%) an alteration of internal architecture of hippocampus was reported. The mean age at the time of HS diagnosis on MRI was 9.5 years (range: 1-18 years).

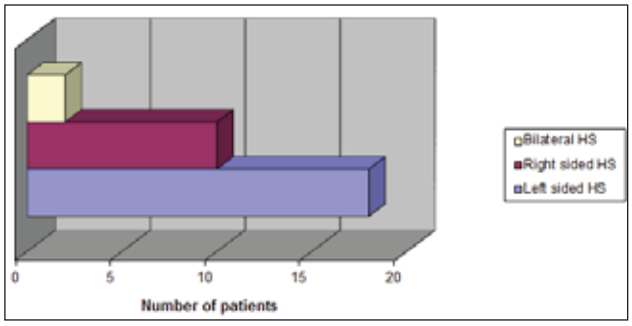

FIGURE 4. *The MRI evidence of HS*

Interictal EEG findings

Two patients presented a normal interictal EEG. Spikes or sharp-waves were found in the anterior temporal areas in 19 patients (63.3%), in extratemporal areas in 12 cases (40%) and with a bilateral

temporal representation in 2 patients (6.6%). Rhythmic theta-delta activity was found in the anterior temporal areas in 10 patients (33.3%) and in extratemporal areas in 6 cases (20%).

Ictal EEG findings

According to the literature, we classified the ictal pattern of temporal seizures in two types. Type one comprised by a rhythmic theta-delta activity, progressively increasing in amplitude, followed by a monomorphic rhythmic theta activity in the temporal derivations. The second type comprised by an initial flattening of temporal background activity, followed by a progressive appearance of the fast activity that spread to the surrounding areas and was followed by a predominant temporal postictal slowing (19).

Seven patients (23.3%) presented the type 1 on ictal EEG recording and 18 patients (60%) presented the type 2.

Interictal and ictal SPECT, interictal FDG-PET, functional MRI

The confirmation of the epileptic focus showed by the MRI and EEG monitoring was made with the help of additional neuroimaging tools. Interictal and ictal SPECT was performed in 17 patients (56.6%) and interictal PET studied was available only for 8 patients (26.6%). The functional MRI was performed in seven children (23.3%) and it demonstrated the dominant hemisphere language representation in five cases and an atypical, bilateral language representation in two cases.

The neuropsychological evaluation

The neuropsychological evaluation was performed extensively for 24 patients (80%) and revealed a normal intellect in 8 patients (26.6%), a borderline IQ in 5 patients (16.6%) and a mental retardation in 11 patients (36.6%). Eleven patients (36.6%) presented a deficit of the verbal memory and 9 patients (30%) a non-verbal memory deficit. A large number of patients exhibit behavioral problems (14 cases, 46.6%) and learning difficulties (19 cases, 63.3%).

The psychopathology was represented by autistic spectrum disorder in 3 patients (including 2 patients that had a genetically confirmed diagnosis of fragile X syndrome) and emotional disorder in one patient.

Surgical treatment

Twenty patients underwent surgical treatment (anterior temporal lobectomy and amigdalohippocampectomy) at the mean age of 12.4 years (range: 4-22 years).

The mean epilepsy duration before surgery was 10.4 years (range: 1-20 years). The patients were treated with a mean number of antiepileptic drugs of 4 (range: 1-10).

Ten patients received only medical treatment, eight of them exhibit a relapsing-remitting course of their epilepsy until the final study follow-up, with at least one interval of minimum one year seizure-free and the other two patients presented drug-resistant epilepsy but they were not eligible for surgical treatment (Figure 5).

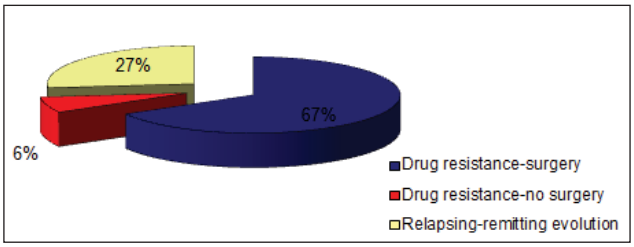

FIGURE 5. *The MTLE-HS evolution in study patients*

The neuropathological evaluation

All surgical patients had histological confirmed HS. Twelve patients presented the classical pattern of HS (HS type 1a) and seven patients had the sever pattern of HS (HS type 1b) (2). One patient associated a dysplasia of temporal neocortex to hippocampal gliosis. All patients presented also different lesional patterns of the dentate gyrus. Furthermore, two patients demonstrated a lesional amygdala (sclerosis in one patient and neuronal loss in other).

The postoperative follow-up

The mean postoperative follow-up was 3 years and 10 months (46 months, range: 6-123 months). The seizure outcome was based on Engel's classification.

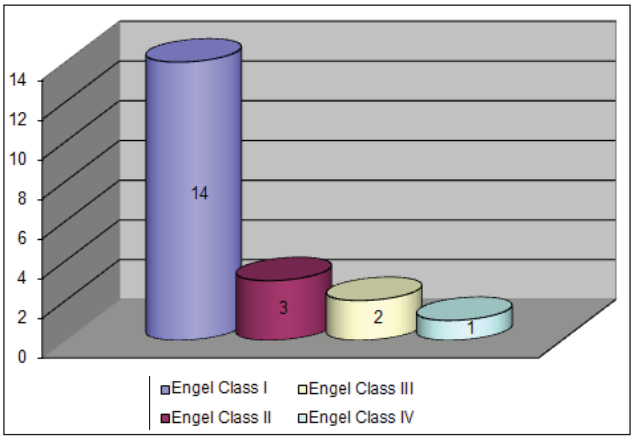

FIGURE 6. *Postoperative seizure outcomes in study patients (Engel class)*

Fourteen patients (70%) disclosed the postoperative seizure outcome in class I Engel (free of disabling seizures), three patients (15%) in class II (rare disabling seizures), two patients in class III and one patient in class IV (persistent seizures with a major or minor reduction of preoperative seizures frequency) (Figure 6).

DISCUSSION

Even if it was considered that a small number of children presented the classical form of MTLE-HS (4-8), recent studies demonstrated the presence of HS in very young children (20, 21). The initial lower prevalence of HS among children (22) could be explained by the difficult detection of HS on routine brain MRIs. Currently, the increasing sensitivity of MRI techniques allowed an early and accurate detection of HS in children (23).

We identified a number of 30 patients with an MRI evidence of HS. This number is analogous to what was reported in others studies of MTLE-HS in children (5, 6, 24, 25). The mean age at the epilepsy onset was 4 years, with the majority of patients distributed in the group II of onset age (2-10 years) according with the dates from previous studies (1,15,26).

Concerning the presence during the personal history of an IPI, 11 patients (36.6%) have a simple or complicated febrile seizure during evolution of their epilepsy. Febrile seizures represented the most frequent mentioned IPI in patients with MTLE-HS (4, 15).

The frequency of febrile seizures largely fluctuated among studies, mostly around 50%-70% (6, 24). The relationship between a history of an early, prolonged febrile seizure and the development of the HS in later life with the concomitant presence of MTLE remains controversial, with most evidences in favor but also against this association (27, 28, 29).In accord with the longitudinal studies, alongside prolonged febrile seizures, other IPI (CNS infections, hypoxia and head trauma) may lead to the development of HS (30).

The presence of a latent and silent period in the patient's evolution of their epilepsy is a strong argument in favor of a progressive course of MTLE (1, 16). In our study group of patients, the latent period had a mean of 39.8 months (3 years 3 months). In the literature, adult studies revealed a mean latent period of 7 years (11). The difference could be explained by the fact that in adult studies of MTLE are included patients with onset of their epilepsy both in childhood and adulthood.

The majority of patients with MTLE-HS exhibit a fluctuated course of the epilepsy, with an initial ingravescent period followed by one of stabilization of seizure disorder severity with a varied duration until the onset of intractability (16). It is likely that the pathogenesis in HS is influenced by genetic and developmental factors (31). In children, temporal lobe epileptogenesis has a great impact on different brain structures that are still maturing (32). It was demonstrated that there are multiple extra-hippocampal grey matter density abnormalities associated with the presence of HS (33). Thus, MTLE could be regard as a neuronal network disease, rather than a focal process (32, 34).

Our group of patients exhibits at the moment of video-EEG monitoring the classical seizure semiology for MTLE-HS with epigastric aura, motor arrest, oroalimentary automatisms and motor lateralizing signs as most reported symptoms. These play an important role in the accurate diagnosis of MTLE-HS. Based on recent evidence, ipsilateral hand automatisms, oroalimentary automatisms and contralateral dystonic posturing can differentiate the mesial temporal lobe seizures associated with HS from those associated with other types of lesions (1). Furthermore, it is very important to distinguish the lateralizing sign and symptoms in MTLE-HS. From these, Todd's paralysis, ictal and postictal aphasia and contralateral posturing of the upper extremity have the highest value (1).

An important aspect of seizure semiology in children is the dynamic changes of semiology along with the advanced in age. The older children demonstrated the classical semiology of MTLE-HS with the same symptoms like adults, but infants and young children presented most subjective and poorly localizing ictal features (17, 19). We also reported that some of the clinical symptoms are dependent of age and in younger children the clinical picture is dominated by motor phenomenon that confirmed the great influence of brain maturation on MTLE-HS (17).

The influence of age could be detected also in the aspect of the interictal EEG. A relative high proportion of our patients demonstrated an extend of epileptiform discharges in extratemporal regions, that is concordant with the dates from the literature (35). In older children, the ictal and interictal abnormalities are similar with that from the adult's studies (15).

The advances made in MRI technique allowed an early and accurate detection of HS. The radiographic features of HS were strictly defined and have been divided into primary and secondary cri-

teria. The primary criteria with the great sensitivity and specificity for HS detection are: hippocampal atrophy, increased hippocampal T2 signal intensity and loss of the internal hippocampal architecture (36). The optimal modality for the inspection of hippocampus is with the help of T2 and FLAIR images in coronal slices perpendicular to the long axis of the hippocampal body (36). In our study, the majority of the patients meet the primary criteria for the MRI diagnosis of HS. Another important aspect is the young age at the MRI detection of HS (mean age 9.5 years) that permitted to choose the best therapeutic option.

The presurgical evaluation of children with MTLE-HS needs to include additional functional neuroimaging techniques. These are ictal and interictal SPECT that can confirm the unilateral temporal involvement and interictal FDG-PET that is the most sensitive neuroimaging technique for the detection of the focal functional deficit associated with HS (37). In our patients, these imaging modalities were available for few patients for that it was necessary to confirm the anterior temporal epileptogenic zone.

The language lateralization and localization was made with the help of functional MRI and these had a great importance in patients with left HS, especially for the prognosis of language deficits after temporal lobectomy (38). From our 7 patients that performed a functional MRI, two patients demonstrated an atypical language representation that is a relative frequent finding in patients with the neuronal damage within the left hemisphere.

The neuropsychological testing is useful for demonstrating the memory and learning disturbances in patients with MTLE-HS and for the evaluation of cognitive evolution in pre and postoperative periods. 11 of the 24 patients that had a standard neuropsychological evaluation presented mental retardation that is relatively similar with the frequency of the intellectual dysfunction detected in a more extended study of children with TLE (39). Intellectual impairment associated with memory deficits and learning problems are the most important risk factors for a worse outcome in MTLE-HS in children and require an early decision for epilepsy surgery (39).

In our study, 20 patients received surgical treatment for their epilepsy at a mean age of 12.4 years and after a mean duration of their epilepsy of 10.4 years. These results are similar with that from children studies (8), but are in contrast with the majority of adult's studies that reported a median time to surgical treatment of approximately 20 years (40). This great difference could be explain by the advances in the presurgical evaluation tools and by the implementation of the accurate defined criteria of children referral to surgical treatment (41).

The results of surgical treatment in our patients were very good, with 14 of 20 patients submitted to surgery that was postoperative seizure free. The percentage of seizure-free patients in childhood epilepsy surgery studies was similar with that reported in adult studies (7, 8). A successful surgical management applied earlier in the course of MTLE-HS in children may avoid the appearance of irreversible psychosocial disturbances and can provide a better quality of life.

CONCLUSIONS

MTLE-HS is a clearly define epileptic syndromic entity and the accurate diagnosis of patients that presented the onset in childhood and adolescence have a great impact in the management of their epilepsy.

We reported the presence of an IPI earlier in the course of MTLE that can influenced the development of HS. The seizure semiology was detailed described because the younger children exhibit some clinical features different from the oldest one. An extensive presurgical evaluation was realized for a better localization of the anterior temporal located epileptogenic zone of which depend the successful of the surgical treatment. We revealed a good postsurgical outcome in the majority of study patients that offer the expectation for a normal life.

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